

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
30 January 2003 (30.01.2003)

PCT

(10) International Publication Number
WO 03/007868 A1

- (51) International Patent Classification⁷: **A61J 1/00**
- (21) International Application Number: **PCT/GB02/03337**
- (22) International Filing Date: **19 June 2002 (19.06.2002)**
- (25) Filing Language: **English**
- (26) Publication Language: **English**
- (30) Priority Data:
0117879.7 **21 July 2001 (21.07.2001)** **GB**
- (71) Applicant (*for all designated States except US*): **COMMON SERVICES AGENCY** [GB/GB]; Trinity Park House, South Trinity Road, Edinburgh EH5 3SE (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **McBAY, William, Edward** [GB/GB]; 41 Shamrock Street, Dunfermline, Fife KY12 0JQ (GB). **WELCH, Anne, Gillian** [GB/GB]; 31 The Firs, Dalgety Bay, Fife KY11 9UH (GB). **McINTOSH, Ronald, Vance** [GB/GB]; 35 Dudley Gardens, Edinburgh EH6 4PR (GB). **FOSTER, Peter, Reynolds** [GB/GB]; 5 St. Stephen Street, Edinburgh EH3 5AN (GB).
- (74) Agents: **MacDOUGALL, Donald, Carmichael et al.**; Cruikshank & Fairweather, 19 Royal Exchange Square, Glasgow G1 3AE (GB).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- *with international search report*
- *with amended claims*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 03/007868 A1

(54) Title: **STORAGE OF LIQUID COMPOSITIONS**

(57) Abstract: Liquid pharmaceutical compositions stored in glass containers, (particularly of blood plasma proteins such as albumin) having a shelf-life in excess of 18 months; over which time the aluminium content is maintained below 200 micrograms per litre. This is achieved by silicone-coating the glass container. Also the particles/ml post-autoclave and post-pasteurisation are kept to low levels.

STORAGE OF LIQUID COMPOSITIONS

The present invention relates to the storage of the liquid pharmaceutical compositions, particularly injectable parenteral compositions, in glass containers in such manner that the aluminium content thereof does not rise above acceptable limits over the storage period and/or whereby the level of particulates contained therein is kept to a minimum.

Aluminium present in injectable solutions is a known clinical problem. In trace amounts, aluminium has been implicated in disorders such as senile dementia of the Alzheimer type, dialysis encephalopathy and kidney damage. For this reason, regulatory authorities have set maximum limits for the aluminium content of injectable pharmaceutical products. For example, the aluminium content of human albumin (generally derived from blood donations) may not exceed 200 micrograms per litre and must be maintained below this level throughout the shelf life of the product. This, however, poses a problem since most injectable solutions are stored in glass containers. Plastic containers are generally not used because of the possibility of leaching plasticisers and unreacted monomer therefrom.

It is, however, known that glass containers tend to leach out aluminium into solutions in contact therewith over extended periods of time, particularly in the case of alkaline solutions. Glasses are typically alumino silicates. Various attempts have been made to address the problem of

aluminium leaching from glass containers over the storage shelf life of injectable solutions.

Kabivitrum patent EP0484464 (WO91/00290) addresses the problem by reducing the initial aluminium content to low levels by diafiltration prior to storage. It is known that different types of glass (identified as type I, II and III) have different properties as regards aluminium leaching. The use of type II glass, which has been treated with sulphur dioxide or ammonium sulphate, is proposed in Green Cross patent application EP559895. However, glass types I and II have been implicated in producing increased aluminium levels in human albumin solutions on extended storage at ambient temperatures (Ray Victor et al, Transfusion 1988, Vol.28, No.3, page 290). Another approach to the maintenance of reduced aluminium levels is set out in Grifols patent application EP0787498, wherein the presence of citrate in albumin solutions is said to increase the rate of leaching of aluminium from glass. The Inventors of this patent application therefore propose the maintenance of reduced citrate levels as a way of mitigating aluminium leaching.

Type II (soft) glass has a lower aluminium content than type I (hard) glass. However, despite using type II glass, the present applicants have continued to experience problems of aluminium accumulation in 20% human albumin solutions, with the 200 microgram per litre limit being exceeded within 18 months.

The problem of particulates in injectable solutions is also a known problem and has been implicated in phlebitis (Allcutt et al., BR. J. Search. Vol. 70 (1983) 111-113). A review of the problem is given in Borchert et al., Journal of Parenteral Science & Technology, Vol.40, No.5/September-October, 1986. In particular, it is found that storage of injectable solutions in glass containers can increase the particulate content thereof, particularly when subject to autoclaving or pasteurisation.

It is an object of the present invention to mitigate the problems of aluminium leaching and/or particulate accumulation in such liquid compositions.

Generally speaking, it has been surprisingly found that siliconisation of glass storage containers mitigates both the problems of aluminium leaching and particle accumulation. Siliconised glass containers are commercially available for other purposes and are generally used to provide a non-wetting surface such that exactly predetermined doses can be dispensed.

Thus, in one aspect the present invention provides a method of storing a liquid pharmaceutical composition susceptible to uptake of aluminium leached from glass containers; which comprises storing the liquid composition in a glass container, whose surface contacting the liquid composition is coated with a silicone coating; whereby uptake of aluminium is mitigated.

Another aspect of the invention provides a storage container which comprises a glass container containing a liquid pharmaceutical composition, the surface of the glass container contacting the liquid composition being coated with a silicone coating.

The liquid pharmaceutical composition is generally an injectable solution which is generally apyrogenic and may have been sterilised by autoclaving or pasteurisation. However, the liquid composition may in principle be any pharmaceutical composition including oral or parenteral compositions, where there is a requirement for reduced aluminium levels to be maintained on storage.

There is a direct relationship between aluminium levels and storage period. Increase in temperature promotes leaching. Generally speaking, the aluminium content should be maintained below 200 micrograms per litre, preferably 150 micrograms per litre, particularly less than 100 micrograms per litre and especially less than 50 micrograms per litre over a storage period (i.e. shelf life) of 12 months, 18 months, 24 months, 36 months, and even up to 48 months; at ambient temperature.

Generally, the pH of the liquid composition will be in the range 4 to 10. Alkaline solutions generally exacerbate the problem of aluminium leaching and are preferably avoided.

The liquid pharmaceutical composition is generally a solution. The present invention is particularly applicable

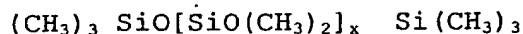
to the storage of blood-derived products, including those derived from human blood donations and those which are produced by recombinant DNA technology. This includes various preparations of plasma proteins such as albumin, plasma protein fraction, transferrin, immunoglobulins, fibrinogen, thrombin, factor VIII, factor IX, factor VII, factor VIIa, von Willibrand factor, factor XIII, antithrombin III, alpha-1-antitrypsin, CI-inhibitor, mannose binding lectin and other protein compositions. However, the invention is in principle applicable to any other liquid pharmaceutical composition where there is a need to maintain low aluminium content.

Aluminium leaching may also be reduced, as is known, by maintaining a low citrate concentration in the liquid composition, for example less than or equal to 0.2 mmol/L, especially less than or equal to 0.1 mmol/L and particularly less than or equal to 0.05 mmol/L.

In particular, at a citrate content of less than 0.25 mmol/L an aluminium content of less than 50 μ mol/L can be maintained at ambient temperature for at least 30 months. At a citrate content of less than 0.1 mmol/L an aluminium content of less than 40 μ mol/L can be maintained at ambient temperature for at least 24 months.

With the siliconisation treatment of the present invention, the type of glass used becomes less critical. Thus, although it is preferred to use soft type II glass, hard type I glass or type III may also be employed.

The siliconisation treatment applied to the glass according to the present invention can be carried out in known manner using any available silicone polymer or prepolymer. The silicone coating can be deposited from solution or suspension or may be created by in situ polymerisation. The coating can be baked at elevated temperature e.g. 300° to 400° to harden the coating and remove extractables. The application of silicone coatings is described, for example, in "Siliconisation of Parenteral Drug Packaging Components" J. Parenteral Sci. Technol. (1988) Vol.42, Suppl.4S, S3-S13; and in Mundry et al., PDA Journal of Pharmaceutical Science & Technology, Vol.54, No.5, September/October 2000. The silicone may be any of those known to be suitable and pharmaceutically acceptable and in particular is a polydimethylsiloxane (linear or cyclic polymer) of the following general formula:



where x for linear polymers can be two to several thousand (e.g. 2 to 5000, particularly 10 to 1000, especially 100 to 500); while x for cyclic polymers is usually 3 to 14 with 4 and 5 being most common. The heat-cured silicones generally have a number average molecular weight or weight average molecular weight in excess of 10,000, possibly in excess of 20,000 and generally in the range 15,000 to 25,000.

It is found that the siliconisation treatment of the glass container also reduces the number of particles shed from

the container surface - leading to reduced particulates in the liquid composition. Previous British Pharmacopoeia Standards set limits of 1,000 particles/mL (for particles greater than or equal to 2 microns) and 100 particles/mL (for particles greater than or equal to 5 microns). These limits are achievable even post-autoclaving or post-pasteurisation employing the siliconised containers of the present invention.

Typically, post-autoclaving the present invention is able to achieve less than 1,000, (generally less than 700) particles per ml for greater than or equal to 2 micron particle size; and less than 75 (generally less than 50) particles per ml for greater than or equal to 5 micron particle size. Post-pasteurisation values achievable are less than 500 particles per ml for greater than or equal to 2 micron particle size and less than 30 particles per ml for greater than or equal to 5 micron particle size.

Thus, the present invention allows aluminium content of liquid compositions to be maintained over an extended shelf life, without the need to resort to any special changes in processing procedures for blood products nor the need to include formulation additives.

Whilst the present invention has been described in relation to the mitigation of aluminium leaching from glass containers, it is equally applicable to the leaching of other metal ions, particularly multivalent metal ions, such as chromium, iron, manganese and nickel.

Embodiments of the present invention will now be described by way of example only in the following examples with reference to attached Figures 1 to 4.

The following Examples relate to the use of siliconised bottles to (a) reduce the contamination of albumin with aluminium during storage in glass bottles and (b) reduce the level of particulate matter in parenteral solutions in glass containers.

Example 1

Human plasma was processed by cold-ethanol (Cohn) fractionation to obtain fraction V precipitate in which $\geq 95\%$ of the total protein was albumin. Fraction V precipitate was resuspended in purified water to a total protein concentration of 80g/L and clarified by depth filtration. The clarified solution was concentrated by ultrafiltration to a protein concentration of 120g/L, diafiltered against 5 volumes of sodium chloride solution (132 mmol/L) to reduce the ethanol concentration to ≥ 8 mg/g protein and then concentrated by ultrafiltration to a protein concentration of about 220 g/L.

The resultant solution was stabilised by the addition of sodium octanoate and adjusted to a protein concentration of 200 g/L prior to membrane filtration to 0.2 μm . Aliquots of

the filtered solution were dispensed aseptically into two types of glass container, either:

(a) 100 mL white type II DIN infusion bottles (supplied by International Bottle Company Ltd),

or

(b) 100 mL white type II DIN infusion bottles with silicone treatment (supplied by International Bottle Company Ltd.). These bottles had been treated with a silicone emulsion, Pharasil E1049 (a 35% oil-in-water emulsion of polydimethylsiloxan) which was sprayed into each bottle. The bottles had then been heated at 400°C in order to fix the silicone to the surface of the glass container.

Following aseptic dispensing of the albumin solution, all bottles were sealed hermetically, subjected to a process of pasteurisation at 60°C for 10 hours and then incubated at 31°C for 14 days.

The citrate content of the Human Albumin product was determined by the enzymatic method of Möllering and Gruber (Analytical Biochemistry 1966; 17: 369-376) using a kit supplied by Boehringer Mannheim. Aluminium was determined by inductively-coupled plasma emission spectroscopy (ICP) using the aluminium line at 167nm.

The aluminium content of the Human Albumin in each type of bottle, ie. container (a) non-siliconised or container (b) siliconised, was monitored during storage at 40°C as an accelerated test of stability and at 25°C as a test of room temperature stability.

The concentration of citrate in the final solution of Human Albumin was 0.25 mmol/L. The concentrations of aluminium at different time points during storage are shown graphically in Figure 1 for storage at 40°C and in Figure 2 for storage at 25°C (the 34 month value for the siliconised bottle is unavailable).

It is evident from these results that the aluminium content of the Human Albumin solution was substantially lower in the siliconised bottles than in the non-siliconised bottles, both at room temperature storage (25°C) and under the accelerated test of storage (40°C).

Example 2

Human albumin was prepared as in Example 1, except that the diafiltration volume was increased from 5 volumes of sodium chloride solution (132 mmol/L) to 7 volumes of sodium chloride solution (132 mmol/L) in order to obtain a lower concentration of citrate in the final product.

The solution of Human Albumin (reduced citrate) was dispensed into non-siliconised and into siliconised bottles as described in Example 1, subjected to pasteurisation at 60°C for 10 hours and incubation at 31°C for 14 days prior to testing for stability at 40°C and at 25°C.

The citrate concentration of Human Albumin (reduced citrate) prepared in this manner was 0.1 mmol/L. The aluminium concentrations at different time points during storage are shown graphically in Figure 3 for storage at 40°C and in Figure 4 for storage at 25°C.

In this experiment, despite the lower concentration of citrate in the protein solution, the Human Albumin (reduced citrate) stored in siliconised bottles exhibited a lower aluminium content than the same batch of product stored in non-siliconised bottles, both under accelerated storage (40°C) and at room temperature storage (25°C).

Example 3

The presence of particulate matter was determined in samples of Water For Injection. Samples of Water For Injection were collected into a particle free cuvette (Accuvette, Coulter Ltd) prior to the product being dispensed into bottles.

The Water For Injection was dispensed into either:

(a) sterile 500mL bottles of type II glass,

or

(b) sterile 500mL bottles of type II glass which had been subjected to a silicone treatment. The silicone treatment involved immersion of the bottles in a siliconising solution, rinsing to remove excess silicone and then fixing of the silicone to the glass surface by baking the bottles at 110°C for 16 hours.

After dispensing the Water For Injection, the bottles were hermetically sealed and the water terminally sterilised by autoclaving for 16 minutes at 121°C under a pressure of 1.15 bar.

Samples from the different bottles were taken into particle free cuvettes (Accuvette, Coulter Ltd) and particle counts/mL were determined semi-automatically for particles $\geq 2\mu\text{m}$ and for particles $\geq 5\mu\text{m}$ according to the electrical zone-sensing method (Coulter Counter).

The results are summarised in Table 1. The data demonstrate an increase in the number of particles after dispensing into standard (non-siliconised) glass bottles and a further increase in the number of particles following sterilisation by

autoclaving at 121°C. By contrast, with siliconised bottles, there was little increase in particulate matter after dispensing into the glass bottle and a smaller increase in the number of particles after heat sterilisation at 121°C. The overall effect was a much lower degree of particulate contamination in Water For Injection contained in siliconised glass bottles compared with that contained in non-siliconised glass bottles.

TABLE 1.

Particles present in Water For Injection using non-siliconise and siliconised bottles

container	stage	n	particles/mL, $\geq 2\mu\text{m}$	Particles/mL, $\geq 5\mu\text{m}$
particle free cuvette	pre-dispensing	5	143 \pm 52	24 \pm 11
non-siliconised bottle	pre-autoclave	12	490 \pm 169	59 \pm 27
siliconised bottle	pre-autoclave	3	183 \pm 73	21 \pm 13
non-siliconised bottle	post-autoclave	11	1266 \pm 398	122 \pm 57
siliconised bottle	post -autoclave	3	362 \pm 169	45 \pm 23

n = number of batches tested

Example 4

As Example 3, using a sterile solution of 9 g/L sodium chloride (Saline) instead of Water For Injection. Table 2 shows the number of particles determined in the different samples taken. As in Example 3, the use of siliconised bottles resulted in little increase in particulate matter after dispensing into the glass bottle and a much lower number of particles after heat sterilisation of the Saline solution at 121°C.

TABLE 2.

Particles present in Saline using non-siliconised and siliconised bottles.

Container	stage	n	particles/mL, $\geq 2\mu\text{m}$	particles/mL, $\geq 5\mu\text{m}$
particle free cuvette	pre-dispensing	2	106	10
non-siliconised bottles	pre-autoclave	7	575 \pm 426	52 \pm 40
siliconised bottles	pre-autoclave	3	125 \pm 25	11 \pm 4
non-siliconised bottles	post-autoclave	12	1301 \pm 332	111 \pm 25
siliconised bottles	post-autoclave	3	606 \pm 208	45 \pm 6

n = number of batches tested

Example 5

As Example 4, except that the bottled Saline was subjected to a process of pasteurisation at 60°C for 10 hours instead of heat sterilisation at 121°C. This was done to simulate the heat treatment that had been applied to solutions of human albumin in Example 1 and Example 2 above in order to examine the effect that this treatment might have on particulate contamination.

The results are summarised in Table 3. Although the impact of pasteurisation at 60°C for 10 hours was less pronounced than autoclaving at 121°C, the degree of particulate contamination was lower when siliconised bottles were used compared with non-siliconised bottles.

Table 3.

Particles present in pasteurised Saline using non-siliconised and siliconised bottles.

container	stage	n	particles/mL, $\geq 2\mu\text{m}$	particles/mL, $\geq 5\mu\text{m}$
non-siliconised bottles	pre-pasteurisation	3	519 \pm 74	53 \pm 19
siliconised bottles	pre-pasteurisation	3	259 \pm 202	17 \pm 11
non-siliconised bottles	post-pasteurisation	3	667 \pm 292	49 \pm 8
siliconised bottles	post-pasteurisation	3	393 \pm 209	20 \pm 11

n = number of batches tested

CLAIMS

1. A method of storing a liquid pharmaceutical composition susceptible to uptake of aluminium leached from glass containers; which comprises storing the liquid composition in a glass container, whose surface contacting the liquid composition is coated with a silicone coating; whereby uptake of aluminium is mitigated.
2. A method according to claim 1 wherein the liquid pharmaceutical composition is an injectable solution.
3. A method according to any preceding claim wherein the liquid pharmaceutical composition comprises human albumin and the aluminium content is less than 200 micrograms per litre.
4. A method according to claim 3 wherein said aluminium content is maintained over a storage period of 12 months at ambient temperature.
5. A method according to claim 4 wherein the storage period is 18 months.
6. A method according to claim 4 wherein the storage period is 24 months.

7. A method according to claim 4 wherein the storage period is 36 months.
8. A method according to any preceding claim wherein the pH of the liquid composition is in the range 4 to 10.
9. A method according to claim 2 wherein the liquid pharmaceutical composition comprises a blood plasma protein.
10. A method according to any preceding claim wherein the liquid composition has a citrate concentration of equal to or less than 0.1 mmol/L.
11. A method according to any preceding claim wherein the glass container is formed of a type II glass.
12. A method according to any preceding claim wherein the silicone coating is produced from a polydimethylsiloxan which has been heated at 400°C.
13. A method according to any preceding claim wherein the liquid composition has less than 700 particles of size greater than or equal to 2 microns per ml. post-autoclaving.

14. A method according to any preceding claim wherein the liquid composition has less than 50 particles of size greater than or equal to 5 microns per ml. post-autoclaving.

15. A method according to any preceding claim wherein the liquid composition has less than 500 particles of size greater than or equal to 2 microns per ml. post-pasteurisation.

16. A method according to any preceding claim wherein the liquid composition has less than 30 particles of size greater than or equal to 5 microns per ml. post-pasteurisation.

17. A storage container which comprises a glass container containing a liquid composition comprising a blood plasma protein and having a shelf life of at least 18 months at ambient temperature, over which time the aluminium content thereof is maintained below 200 micrograms per litre; the surface of the glass container contacting the liquid composition being coated with a silicone coating.

18. A container according to claim 17 wherein the blood plasma protein is human albumin.

AMENDED CLAIMS

[received by the International Bureau on 09December 2002 (09.12.02);
original claims 1-18 replaced by new claims 1-18]

1. A method of storing a liquid pharmaceutical composition susceptible to uptake of aluminium leached from glass containers; which comprises storing the liquid composition over a storage period of 12 months at ambient temperature in a glass container, whose surface contacting the liquid composition is coated with a silicone coating;

whereby uptake of aluminium is mitigated such that the aluminium content is maintained below 200 micrograms per litre.

2. A method according to claim 1 wherein the liquid pharmaceutical composition is an injectable solution.

3. A method according to any preceding claim wherein the liquid pharmaceutical composition comprises human albumin.

4. A method according to any preceding claim wherein said aluminium content is maintained over a storage period of 18 months at ambient temperature.

5. A method according to claim 4 wherein the storage period is 24 months.

6. A method according to claim 4 wherein the storage period is 36 months.

7. A method according to claim 4 wherein the storage period is 48 months.

8. A method according to any preceding claim wherein the pH of the liquid composition is in the range 4 to 10.
9. A method according to claim 2 wherein the liquid pharmaceutical composition comprises a blood plasma protein.
10. A method according to any preceding claim wherein the liquid composition has a citrate concentration of equal to or less than 0.1 mmol/L.
11. A method according to any preceding claim wherein the glass container is formed of a type II glass.
12. A method according to any preceding claim wherein the silicone coating is produced from a polydimethylsiloxane which has been heated at 400°C.
13. A method according to any preceding claim wherein the liquid composition has less than 700 particles of size greater than or equal to 2 microns per ml. post-autoclaving.
14. A method according to any preceding claim wherein the liquid composition has less than 50 particles of size greater than or equal to 5 microns per ml. post-autoclaving.
15. A method according to any preceding claim wherein the liquid composition has less than 500 particles of size greater than or equal to 2 microns per ml. post-pasteurisation.

16. A method according to any preceding claim wherein the liquid composition has less than 30 particles of size greater than or equal to 5 microns per ml. post-pasteurisation.

17. A storage container which comprises a glass container containing a liquid composition comprising a blood plasma protein and having a shelf life of at least 18 months at ambient temperature, over which time the aluminium content thereof is maintained below 200 micrograms per litre; the surface of the glass container contacting the liquid composition being coated with a silicone coating.

18. A container according to claim 17 wherein the blood plasma protein is human albumin.

Fig 1. Effect of Siliconised Bottles on Aluminium in 20% Human Albumin Stored at 40°C.

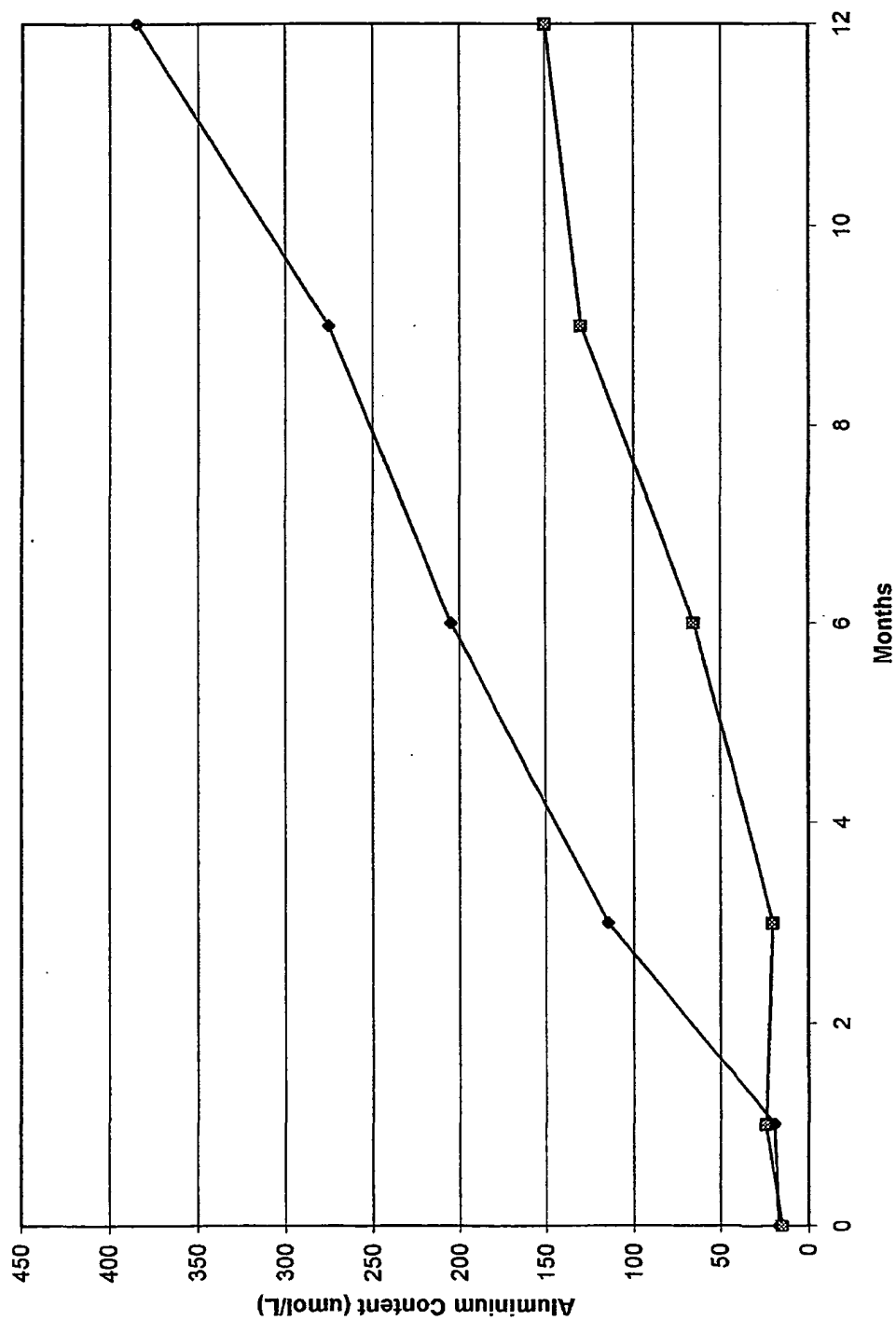
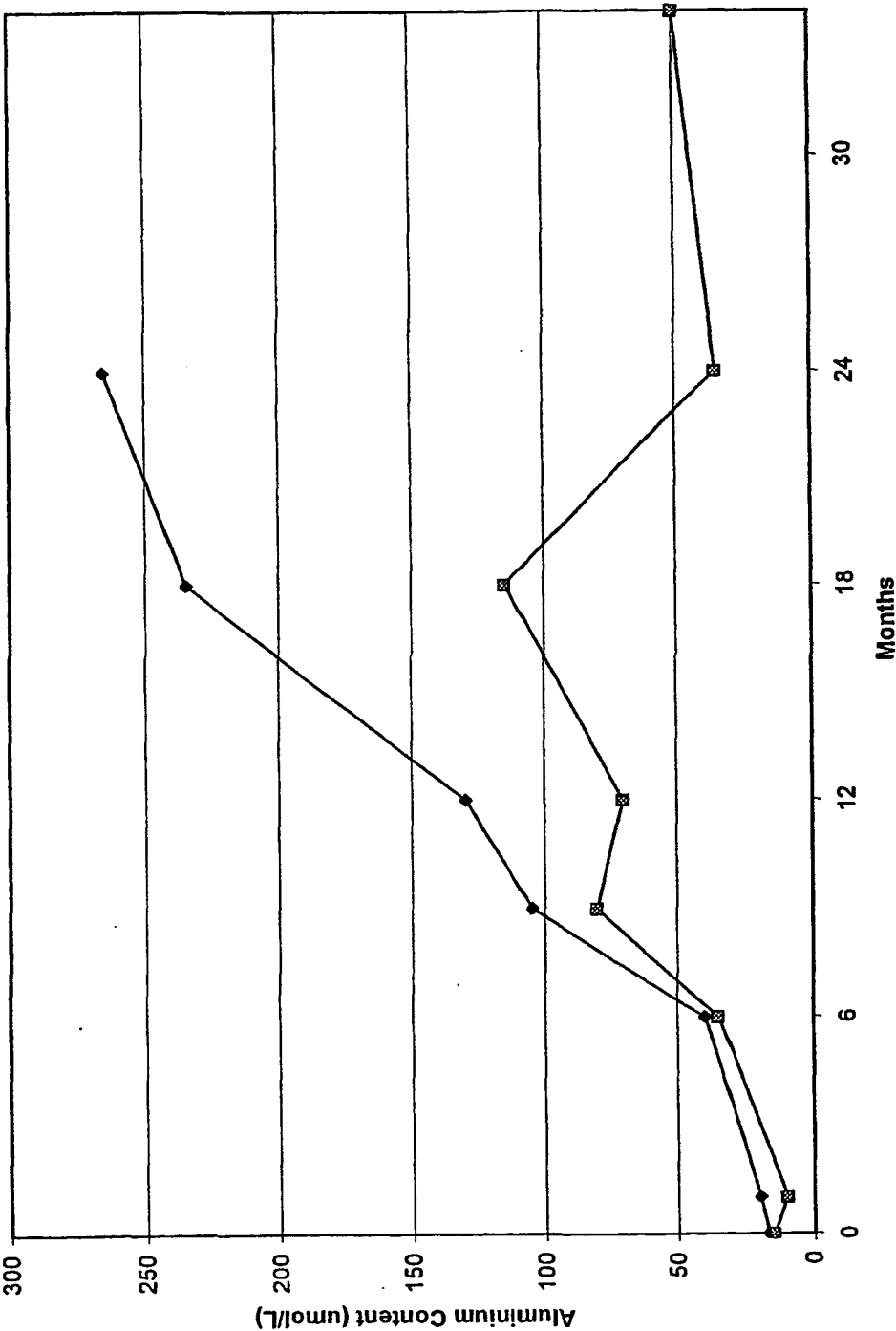


Fig 2. Effect of Siliconised Bottles on Aluminium in 20% Human Albumin Stored at 25°C.



3/4

Fig 3. Effect of Siliconised Bottles on Aluminium in 20% Human Albumin (reduced citrate) on Storage at 40°C.

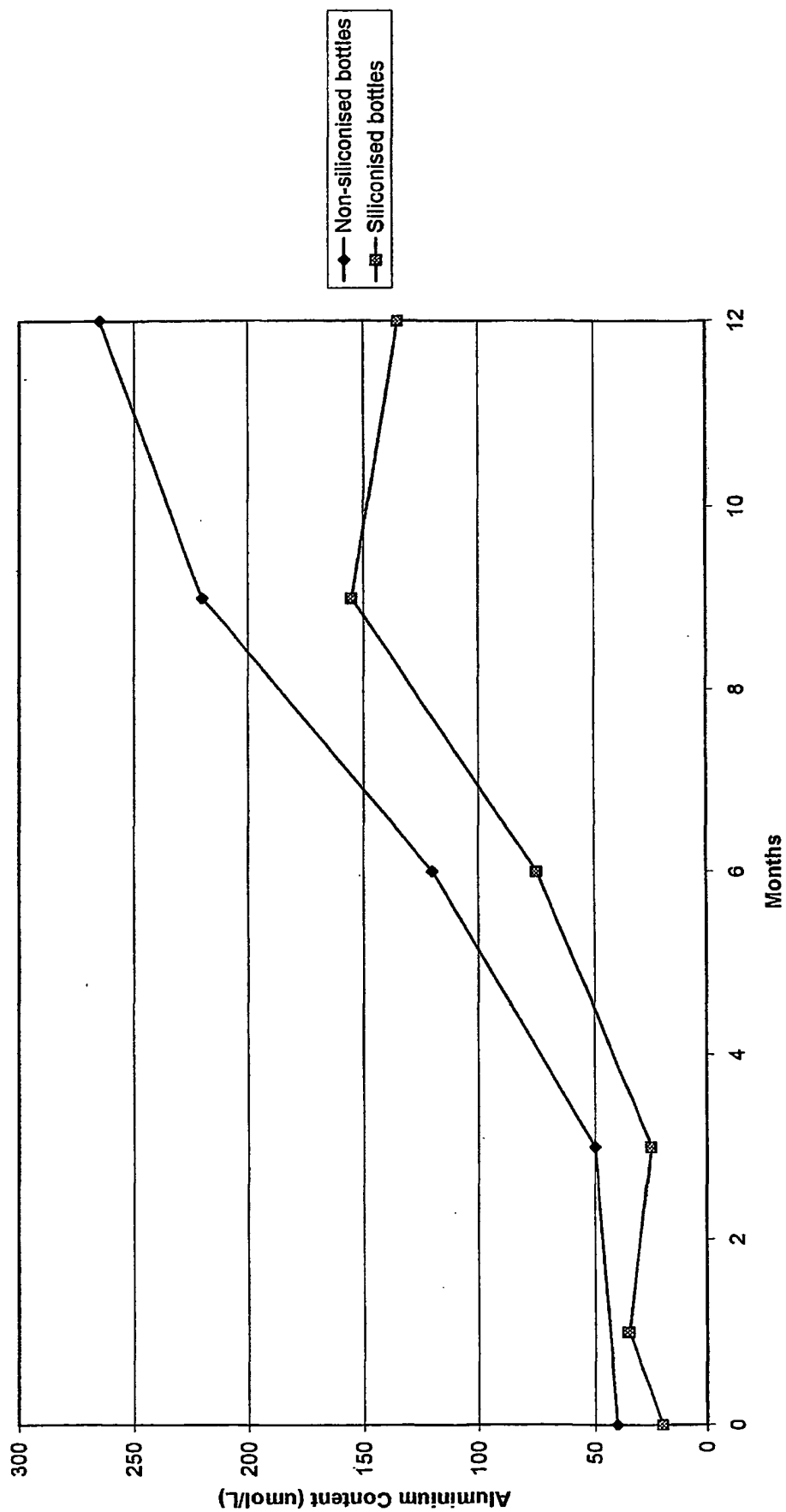
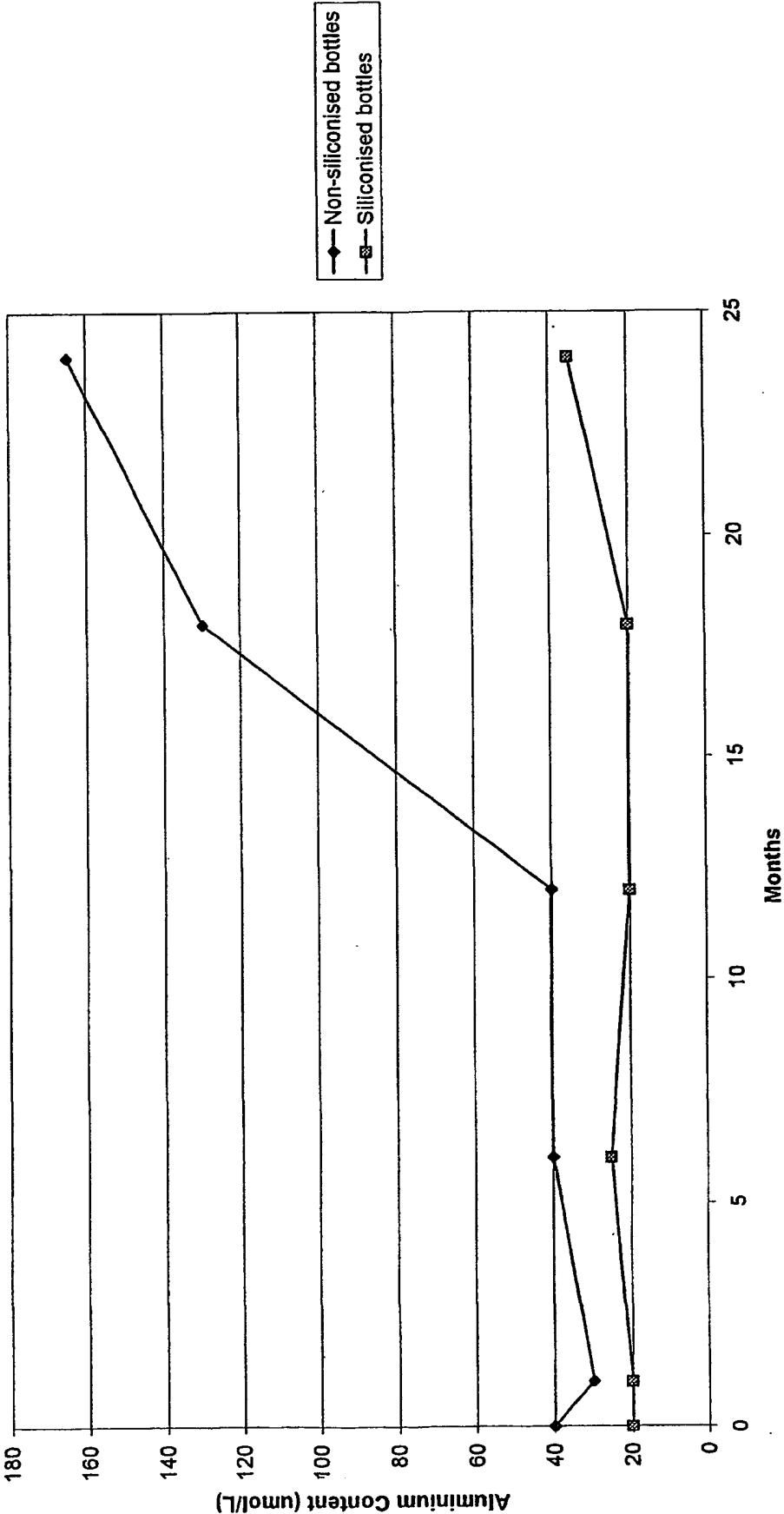


Fig 4. Effect of Siliconised Bottles on Aluminium in 20% Human Albumin (reduced citrate) Stored at 25°C.



INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/GB 02/03337

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61J1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61J B65D A61L C03C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 982 041 A (MEDTRONIC AVE INC) 1 March 2000 (2000-03-01) page 6, line 22 - line 31	1-18
X	EP 0 698 398 A (BECTON DICKINSON CO) 28 February 1996 (1996-02-28) column 5, line 56 -column 6, line 12; figure 2	1-18
X	EP 0 080 908 A (BECTON DICKINSON CO) 8 June 1983 (1983-06-08) the whole document	1-18

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date-
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

30 September 2002

Date of mailing of the international search report

09/10/2002

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Godot, T

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internati Application No

PCT/GB 02/03337

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0982041	A	01-03-2000	US 6248127 B1	19-06-2001
			EP 0982041 A1	01-03-2000
			US 6361819 B1	26-03-2002
			US 2001034336 A1	25-10-2001
EP 0698398	A	28-02-1996	EP 0698398 A1	28-02-1996
			JP 2749289 B2	13-05-1998
			JP 8275932 A	22-10-1996
EP 0080908	A	08-06-1983	US 4529614 A	16-07-1985
			AU 553928 B2	31-07-1986
			AU 8940582 A	09-06-1983
			DE 3265662 D1	26-09-1985
			EP 0080908 A1	08-06-1983
			JP 1664483 C	19-05-1992
			JP 3023178 B	28-03-1991
			JP 58097367 A	09-06-1983
			NZ 202357 A	14-12-1984